DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Thomas K. Rogers
Executive Vice President, Regulatory Affairs
King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, TN 37620

JUN 18 2008

Re: Docket No. FDA-2008-P-0304

Dear Mr. Rogers:

This responds to your citizen petition dated May 16, 2008 (Petition), regarding cardiovascular outcomes labeling for certain drug products referencing Altace (ramipril) capsules or tablets (Altace products) for the treatment of hypertension. Your Petition requests that the Food and Drug Administration (FDA or the Agency) confirm that label information describing cardiovascular outcomes from the Heart Outcomes Prevention Evaluation (HOPE) trial[1] and the related indication may not be omitted from the labeling of any abbreviated new drug application (ANDA) submitted under 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)) (the Act) or new drug application (NDA) submitted through the approval pathway described by section 505(b)(2) of the Act (21 U.S.C. 355(b)(2)) (505(b)(2) application) that relies upon an Altace product and seeks approval for the treatment of hypertension. Accordingly, the Petition seeks to confirm that ANDAs and 505(b)(2) applications that reference an Altace product must contain an appropriate patent certification to U.S. Patent Number 7,368,469 (the '469 patent), which has been listed as a method-of-use patent for Altace products in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book), and may not contain a statement pursuant to section 505(b)(2)(B) or 505(j)(2)(A)(viii) of the Act explaining that the patent does not claim a use for which the applicant is seeking approval.

We have carefully reviewed your Petition and have concluded that ANDA and 505(b)(2) applicants seeking approval of ramipril products can omit from the product labeling the information from Altace labeling related to a reduction in risk of myocardial infarction, stroke, and death from cardiovascular causes (the HOPE indication) without rendering the proposed drug product less safe or effective than Altace products for the remaining conditions of use (treatment of hypertension and use in heart failure post-myocardial infarction). For the reasons described in further detail in this response, your Petition is denied.

[1] See The Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. "Effects of an Angiotensin-Converting-Enzyme Inhibitor, Ramipril, on Cardiovascular Events in High-Risk Patients." N Engl J Med 2000;342:145-53 (HOPE Study article).

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I. BACKGROUND

A. Ramipril Products

Ramipril is an angiotensin-converting-enzyme (ACE) inhibitor. Altace (ramipril) capsules (NDA 19-901) were approved for the treatment of hypertension in 1991, and for use in patients with heart failure post-myocardial infarction in 1995.

In October 2000, King Pharmaceuticals, Inc. (King), the current NDA holder, received approval for use of Altace capsules to reduce the risk of myocardial infarction, stroke, and death from cardiovascular causes in a specified patient population at high risk of having a major cardiovascular event. As discussed in more detail below, this indication was based on data from the HOPE trial and is referred to as *the HOPE indication*. King received 3 years of marketing exclusivity (which expired on October 4, 2003) in connection with the HOPE trial for use of ramipril for reduction in risk of myocardial infarction, stroke, and death from cardiovascular causes (see section 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the Act). On February 27, 2007, Cobalt Pharmaceuticals, Inc. (Cobalt) obtained approval for a tablet dosage form of Altace (NDA 22-021) for use in each of these indications.[2]

On October 24, 2005, Cobalt received approval for the first ANDA for ramipril capsules (ANDA 76-549) for treatment of hypertension and the HOPE indication.[3] Pursuant to section 505(j)(5)(B)(iv) of the Act, Cobalt was granted a 180-day period of marketing exclusivity that expired on Saturday, June 7, 2008, in connection with its patent challenge of U.S. Patent Number 5,061,722 listed for Altace capsules.[4]

On May 6, 2008, subsequent to approval of Cobalt's ANDA, the '469 patent was issued by the Patent and Trademark Office. King timely submitted information on the '469 patent to FDA for listing in the Orange Book as a method-of-use patent claiming Altace products (see section 505(c)(2) of the Act). The use code listed in the Orange Book for the '469 patent reflects King's description of this patent as claiming a method of reducing the risk of myocardial infarction, stroke, and death. This use corresponds to the HOPE indication and related information regarding the HOPE trial in Altace product labeling.

As we discuss below, the timing of approvals for ANDAs and 505(b)(2) applications is subject to the patent and marketing exclusivity protections accorded the listed drug relied upon.

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[2] This NDA subsequently was transferred to King, the current NDA holder for Altace tablets.

[3] Cobalt did not seek approval of ramipril capsules for use in patients with heart failure post-myocardial infarction, an indication for which a method-of-use patent (U.S. Patent Number 5,403,856 expiring April 4, 2012) is listed in the Orange Book for Altace capsules. See letter dated January 29, 2008, from Gary Buehler, R.Ph., Director, Office of Generic Drugs to Carmen Shepard, Esq. and Kate Beardsley, Esq. (Docket No. 2007N-0382) at 3, note 3. Docket number 2007N-0382 was changed to FDA-2007-N-0035 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[4] Cobalt's ANDA for ramipril capsules was approved prior to listing of the '469 patent in the Orange Book. Accordingly, Cobalt was not required to submit a patent certification or statement to the '469 patent (see 21 CFR 314.94(a)(12)(viii)(C)(*2*)) and its labeling is the same as the reference listed drug with respect to the HOPE indication.

B. Abbreviated Approval Pathways Available Under the Act

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(b)(2) and 505(j) of the Act. The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962" with new incentives for drug development in the form of marketing exclusivity and patent term extensions.[5] Section 505(j) of the Act established an abbreviated approval pathway for a drug product that is the same as a previously approved drug (the reference listed drug) with respect to active ingredient, dosage form, route of administration, strength, labeling, and conditions of use, among other characteristics. An ANDA applicant also must demonstrate that its proposed product is bioequivalent to the reference listed drug. An applicant that can meet the requirements under section 505(j) for approval may reference the Agency's finding of safety and effectiveness for the reference listed drug, and need not repeat the extensive nonclinical and clinical investigations required for approval of a stand-alone NDA submitted under section 505(b)(1) of the Act.

Section 505(b)(2) of the Act describes an application that contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use. A 505(b)(2) applicant may rely on FDA's finding of safety and effectiveness for a listed drug only to the extent that the proposed product in the 505(b)(2) application shares characteristics (e.g., active ingredient, dosage form, route of administration, strength, indication, conditions of use) in common with the listed drug. To the extent that the listed drug and the drug proposed in the 505(b)(2) application differ, the 505(b)(2) application must include sufficient data to demonstrate that the proposed drug meets the statutory approval standard for safety and effectiveness. The product labeling for a drug approved through the 505(b)(2) pathway need not be the same as the listed drug relied upon.

The remainder of this discussion will address patent certification and labeling requirements for ANDAs and the permissibility of omitting the HOPE indication and related information from the proposed labeling of an ANDA for ramipril products. Similar considerations would apply to a 505(b)(2) application that sought to rely upon the Agency's finding of safety and effectiveness for Altace products and sought to omit information regarding the HOPE trial from product labeling. As noted above, however, a 505(b)(2) application is not required to have the same labeling as the listed drug it references.

C. Patent Certification Requirements for an ANDA

An ANDA applicant must include an appropriate patent certification or statement for each patent that claims the reference listed drug or a method of using the drug for which the applicant is seeking approval and for which information is required to be filed under section 505(b)(1) or

[5] See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

505(c)(2) of the Act.[6] For each patent listed in the Orange Book, the ANDA applicant must submit one of the following:

- a certification that the patent will expire on a specific date (delaying approval until the date on which such patent will expire) (paragraph III certification) (section 505(j)(2)(A)(vii)(III) of the Act);
- a certification that the patent is invalid or will not be infringed by the manufacture, use, or sale of the drug product for which the ANDA is submitted (paragraph IV certification) (section 505(j)(2)(A)(vii)(IV) of the Act); or,
- with respect to a method-of-use patent, a statement that the patent does not claim a use for which the ANDA applicant is seeking approval (section viii statement) (section 505(j)(2)(A)(viii) of the Act).

An applicant submitting a paragraph IV certification is required to give notice of the patent challenge to the holder of the NDA for the reference listed drug and each owner of the patent that is the subject of the certification. Notice of a paragraph IV certification is intended to provide an opportunity for "any legal disputes regarding the scope of the patent and the possibility of infringement [to] be resolved as quickly as possible" (*Torpharm, Inc. v. Thompson,* 260 F. Supp. 2d 69, 71 (D.D.C. 2003), *aff'd*, 354 F.3d 877 (D.C. Cir. 2004)). In most cases, if the NDA holder or patent owner initiates a patent infringement action within 45 days after receiving notice of the paragraph IV certification, there will be a statutory 30-month stay of approval of the ANDA while the patent infringement litigation is pending (section 505(j)(5)(B)(iii) of the Act).[7]

The first applicant to submit a substantially complete ANDA containing a paragraph IV certification may be eligible for a 180-day period of marketing exclusivity during which approval of subsequent ANDAs for the same drug product that also contain a paragraph IV certification to the patent will not be granted. The 180-day exclusivity period described in section 505(j)(5)(B)(iv) of the Act provides an incentive for ANDA applicants to challenge listed patents that may be invalid, unenforceable, or not infringed by the drug product described in the ANDA.

An ANDA applicant seeking to omit an approved method of use covered by a listed patent need not file a paragraph III or paragraph IV certification for that patent. Instead, the applicant may submit a section viii statement acknowledging that a method-of-use patent has been listed, but explaining that the patent does not claim a use for which the applicant seeks approval (see section 505(j)(2)(A)(viii) of the Act). Such a statement requires the ANDA applicant to omit or "carve out" from its labeling information pertaining to the protected use (see 21 CFR

[6] The NDA holder for a listed drug such as Altace capsules is required to submit information to FDA on "any patent which claims the drug . . . or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture[,] use, or sale of the drug" (see section 505(b)(1) and 505(c)(2) of the Act).

[7] However, if patent information for the reference listed drug is submitted by the NDA holder after the date on which an ANDA is submitted (that FDA later determines to be substantially complete), a 30-month stay is not available (see section 505(j)(5)(b)(iii) of the Act).

314.92(a)(1) and 314.94(a)(12)(iii)).[8] If an ANDA applicant files a section viii statement, the patent claiming the protected method of use will not serve as a barrier to ANDA approval.[9] The right to file a section viii statement and carve out from labeling method-of-use information protected by a patent has been upheld by the courts.[10] In addition, an ANDA's 180-day exclusivity period would not preclude approval of a subsequent ANDA referencing the same listed drug if the subsequent ANDA contains a section viii statement with respect to the patent upon which 180-day exclusivity was based and omits from the labeling information related to the use protected by the patent.

D. Labeling Requirements for Products Approved in ANDAs

Section 505(j)(2)(A)(i) of the Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]." This language reflects Congress's intent that the generic drug be safe and effective for each "condition of use" prescribed, recommended, or suggested in the generic drug labeling. However, it does not require that an ANDA be approved for each condition of use for which the reference listed drug is approved. Our regulations in 21 CFR 314.92(a)(1) explicitly state that a proposed generic drug product must have the same conditions of use as the listed drug, except that "conditions of use for which approval cannot be granted because of . . . an existing *patent* may be omitted" (emphasis added).

The Act also requires that an ANDA contain "information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug. . . except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the Act] or because the new drug and the listed drug are produced or distributed

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[8] See also "Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed; Final Rule" (68 FR 36676 at 36682, June 18, 2003). In the preamble to this final rule, we stated that the section viii statement permits an ANDA applicant to "avoid certifying to a patent by stating that it is not seeking approval for the use claimed in the listed patent." We further stated that "[o]ur position has been that, for an ANDA applicant to file a section viii statement, it must 'carve-out' from the proposed ANDA labeling, the labeling protected by the listed patent." It should be noted that certain sections of this final rule regarding the application of 30-month stays on approval of certain ANDAs and 505(b)(2) applications were superseded by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) (Public Law 108-173) and revoked by technical amendment (69 FR 11309, March 10, 2004).

[9] The Agency's interpretation of the plain language of the Act is further supported by Congressional intent as evidenced by the passage below:

> . . . The [ANDA] applicant need not seek approval for all of the indications for which the listed drug has been approved. For example, if the listed drug has been approved for hypertension and angina pectoris, and if the indication for hypertension is protected by patent, then the applicant could seek approval for only the angina pectoris indication.

House Report No. 98-857, part 1, at 21 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2654.

[10] See *Purepac Pharmaceutical Company v. Thompson,* 354 F.3d 877, 880 (D.C. Cir. 2004) (stating that a "section viii statement indicates that a patent poses no bar to approval of an ANDA because the applicant seeks to market the drug for a use other than the one encompassed by the patent"); *Torpharm,* 260 F. Supp. 2d at 73 (stating that a section viii statement "avers that the patent in question has been listed, but does not claim a use for which the applicant seeks FDA approval").

by different manufacturers" (section 505(j)(2)(A)(v) of the Act; see also 21 CFR 314.94(a)(8)(iv)). A parallel provision appears in section 505(j)(4)(G) of the Act.[11] Section 314.94(a)(8)(iv) sets forth examples of permissible differences in labeling that may result because the generic drug product and reference listed drug are produced or distributed by different manufacturers. These differences include the following:

> . . .differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or *omission of an indication or other aspect of labeling protected by patent* or accorded exclusivity under section 505(j)(4)(D) of the Act[12] (emphasis added).

The regulations at 21 CFR 314.127(a)(7) further provide that to approve an ANDA containing proposed labeling that omits "aspects of the listed drug's labeling [because those aspects] are *protected by patent*," we must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining non-protected conditions of use" (emphasis added).

Relevant case law affirms an ANDA applicant's ability to carve out protected labeling without violating the "same labeling" requirement. For example, in *Bristol Myers Squibb v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996), the D.C. Circuit ruled that "the statute expresses the legislature's concern that the new generic be safe and effective for each indication that will appear on its label; whether the label for the new generic lists every indication approved for the use of the pioneer is a matter of indifference." This case involved Capoten (captopril), another ACE inhibitor, and upheld FDA's determination that an ANDA applicant for captopril may omit the indications protected by exclusivity (left ventricular dysfunction following myocardial infarction and diabetic nephropathy in patients with Type I insulin-dependent diabetes mellitus and retinopathy) and the corresponding protected, indication-specific dosing information. Similarly, in *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141, 148, n. 3 (4th Cir. 2002), the Fourth Circuit upheld the right of an ANDA applicant to carve out an indication protected by orphan drug exclusivity as a permissible difference due to difference in manufacturer.

Thus, the statute, regulations, and applicable case law permit the omission of an indication or other aspect of labeling protected by a listed patent as an acceptable difference between an ANDA and the reference listed drug that are produced or distributed by different manufacturers if the omission does not render the proposed ANDA less safe or effective for the conditions of use that remain in the labeling.

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[11] Section 505(j)(4)(G) of the Act provides that FDA must approve an ANDA unless, among other things, "the information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for [the reference listed drug] except for changes required because of differences approved under [an ANDA suitability petition] or because the drug and the listed drug are produced or distributed by different manufacturers."

[12] We note that, due to a series of amendments to the Act, the reference in § 314.94(a)(8)(iv) to section 505(j)(4)(D) of the Act corresponds to current section 505(j)(5)(F) of the Act.

II. ANALYSIS

You request confirmation that FDA will require all ANDAs (and 505(b)(2) applications) for ramipril products that seek approval for treatment of hypertension to include information on cardiovascular outcomes from the HOPE trial in product labeling (Petition at 4). You maintain that the "HOPE information is intertwined with hypertension" and that omission of HOPE information from product labeling for a generic ramipril product would render the product less safe and less effective for treating hypertension than Altace (Petition at 4 and 7). In support of your argument, you reference the June 15, 2005, and April 26, 2006, meetings of FDA's Cardiovascular and Renal Drugs Advisory Committee and the draft guidance[13] recently published by the Agency regarding the inclusion of cardiovascular outcome data in the labeling for anti-hypertensive drug products (Petition at 4). We address your arguments below.[14]

A. The HOPE Trial Was Not Primarily An Assessment of Ramipril's Ability to Alter Cardiovascular Outcomes in a Hypertensive Population

The HOPE trial evaluated the effects of ramipril in preventing the composite outcome of death from cardiovascular causes, myocardial infarction, or stroke in a population considered to be at high risk for cardiovascular events.[15] The population studied in the HOPE trial was composed of individuals at least 55 years old with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes plus at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low high-density lipoprotein cholesterol levels, cigarette smoking, or documented microalbuminuria). The results of the HOPE trial demonstrated that individuals considered to be at high risk for cardiovascular events (generally not hypertensive at

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[13] Draft guidance for industry on *Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims* (March 2008), available at http://www.fda.gov/cder/guidance/index.htm under Labeling.

[14] The Agency has determined previously that information in Altace product labeling related to use in heart failure post-myocardial infarction

> may be omitted from the labeling of a generic product without rendering the proposed drug product less safe or effective than the listed drug for the remaining, nonprotected conditions of use, (i.e., the reduction in risk of myocardial infarction, stroke and death from cardiovascular causes, and the treatment of hypertension)... because the benefit with the excluded use is independent of that of the other uses and because the observed nominal differences in the reported adverse events are largely artifacts of sampling.

Letter dated October 21, 2005, from Norman Stockbridge, M.D., Ph.D., Acting Director, Division of Cardiovascular and Renal Products, to King Pharmaceuticals, Inc., in response to King's letter dated January 26, 2005, suggesting that FDA reject any proposed labeling for a generic ramipril product that omitted information related to one or more clinical studies (including the Acute Infarction Ramipril Efficacy (AIRE) trial supporting the heart failure post-myocardial infarction indication and the HOPE trial) described in Altace product labeling (see Petition at 7).

As the HOPE indication was included in Altace product labeling at the time of the Agency's previous determination regarding the availability of a "carve-out" of the indication for heart failure post-myocardial infarction, our response to this Petition addresses whether the HOPE indication may be omitted from the labeling of a generic ramipril product that seeks approval for the treatment of hypertension, with or without the indication for heart failure post-myocardial infarction.

[15] See HOPE Study article. The HOPE trial also evaluated the effects of Vitamin E on cardiovascular outcomes, in a two-by-two factorial study design.

baseline) who received ramipril (10 milligrams (mg) per day) had a 22 percent reduction in risk of the composite outcome of myocardial infarction, stroke, or death from cardiovascular causes as compared to placebo (relative risk: 0.78; 95 percent confidence interval: 0.70-0.86; $p<0.001$).

Although you emphasize that "[n]early half of the patients in HOPE were hypertensive (n=4355)" (Petition at 2), it should be noted that the entry criteria for the HOPE trial only required a *history* of hypertension as an acceptable additional risk factor. This did not necessarily mean that subjects in the HOPE trial were currently hypertensive and/or untreated for hypertension.[16] The mean baseline blood pressure for study participants at study entry was 139/79 mmHg, and the mean blood pressure at the end of the study (up to approximately 5 years of observation) was 136/76 mmHg in the ramipril group and 139/77 mmHg in the placebo group.

The HOPE Study Investigators concluded that "[o]nly a small part of the benefit could be attributed to a reduction in blood pressure, since the majority of patients did not have hypertension at base line (according to conventional definitions) and the mean reduction in blood pressure with treatment was extremely small (3/2 mmHg)."[17] In his June 15, 2005, testimony before the Cardiovascular and Renal Drugs Advisory Committee regarding class labeling for antihypertensive drugs, Dr. Charles Pamplin, Vice President for Medical Affairs at King, similarly noted that the HOPE trial "was not primarily a hypertensive study."[18] Dr. Pamplin further stated that

> outcomes data from HOPE indicates a similar risk reduction benefit in patients who were either normotensive, the majority of the patients I might add, or who were controlled hypertensives. Therefore, while ramipril does reduce blood pressure, the majority of its benefit on cardiovascular risk reduction cannot be attributed solely [to] an antihypertensive effect. Thus, to extrapolate its cardiovascular morbidity and mortality benefits to other agents solely on the basis for reduction in blood pressure may be inappropriate.[19]

King does not appear to have abandoned its view that the HOPE study supports a specific benefit in high-risk patients not attributable to its blood pressure effects, a view that led to seeking approval for a separate indication for Altace for "reduction in risk of myocardial infarction, stroke, and death from cardiovascular causes" based on the results of the HOPE trial. Although King maintains that outcomes data for ramipril from the HOPE trial "have contributed to the overall conclusion that reducing hypertension can be related to improved cardiovascular

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[16] Uncontrolled hypertension or overt nephropathy were among the exclusion criteria for the HOPE trial. Other exclusion criteria for the study were heart failure, known low ejection fraction (<0.40), current ACE inhibitor or vitamin E use, or history of "a myocardial infarction or stroke within four weeks before the study began" HOPE Study article.

[17] HOPE Study article.

[18] Food and Drug Administration, Cardiovascular and Renal Drugs Advisory Committee meeting transcript, June 15, 2005 at 216, available on the Internet at http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4145T1.pdf (2005 Advisory Committee Transcript).

[19] 2005 Advisory Committee Transcript at 217.

outcomes" (Petition at 4), it has not proposed revisions to the hypertension indication for Altace.[20]

King further requests that FDA confirm that it will "continue to approve ramipril products for the treatment of hypertension only with complete and accurate label information regarding the outcomes associated with treating hypertensive and non-hypertensive patients as described in the label information obtained from the HOPE trial" (Petition at 1 to 2). King's description of the HOPE information in Altace product labeling as including "the beneficial cardiovascular outcomes obtained when hypertensive patients are treated with Altace" (Petition at 2) appears to refer to the subgroup analysis in Figure 2 ("The Beneficial Effect of Treatment with Ramipril on the Composite Outcome of Myocardial Infarction, Stroke, or Death from Cardiovascular Causes Overall and in Various Predefined Subgroups"), which was reproduced from the article in the *New England Journal of Medicine* describing the HOPE study results.[21] However, given that the effect of ramipril on the composite outcome of myocardial infarction, stroke, or death from cardiovascular causes did not materially differ among patients with and without a history of hypertension treated with ramipril, the HOPE trial does not provide cardiovascular outcomes data specific to the hypertension indication.

B. Omission of the HOPE Indication Does Not Render Ramipril Less Safe or Effective for the Treatment of Hypertension.

King contends that the HOPE trial "contains information relevant to the treatment of hypertensive patients" (Petition at 4). As discussed below, each of the sections of Altace labeling identified by King as related to the method of using the drug product claimed by the '469 patent may be omitted from product labeling for a generic ramipril product seeking approval for the treatment of hypertension without rendering the generic ramipril product less safe or effective than Altace for the hypertension indication.

1. Indications and Usage

The HOPE indication in Altace product labeling states the following:

> **Reduction in Risk of Myocardial Infarction, Stroke, and Death from Cardiovascular Causes**
>
> Altace is indicated in patients 55 years or older at high risk of developing a major cardiovascular event because of a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes that is accompanied by at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low HDL levels, cigarette smoking, or documented microalbuminuria), to reduce the risk of myocardial infarction, stroke, or

[20] If King now believes that the beneficial effect of ramipril on cardiovascular outcomes in the high-risk population described in the HOPE trial was attributable to a reduction in blood pressure, King should submit a supplement to their NDA clarifying the source of ramipril's effect on cardiovascular outcomes in the HOPE trial and requesting appropriate revisions to Altace product labeling. FDA cannot opine on whether it would approve such a supplement until it has had a chance to review it.

[21] See HOPE Study article.

death from cardiovascular causes. Altace can be used in addition to other needed treatment (such as antihypertensive, antiplatelet or lipid-lowering therapy).

As discussed in section II.A of this response, the populations covered by the HOPE indication and the hypertension indication are not the same. The HOPE population was composed of patients at least 55 years old with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes, plus at least one of five other cardiovascular risk factors, which included hypertension. In fact, fewer than half the patients participating in the HOPE study had hypertension.[22] Moreover, the use of ramipril in the HOPE trial was not directed at the control of blood pressure. Indeed, the HOPE indication in Altace labeling states that "Altace can be used in addition to other needed treatment (such as antihypertensive... therapy)."

Although you assert that the HOPE label information "identifies the particular patient populations expected to benefit from more aggressive treatment" (Petition at 9), we note that the HOPE indication identifies a population at high risk of developing a major cardiovascular event (and generally not hypertensive at study baseline). Ramipril was not used in the HOPE trial for the treatment of hypertension, and the HOPE indication may be omitted from the INDICATIONS AND USAGE section of labeling for a generic ramipril product that seeks approval for the treatment of hypertension.

2. Pharmacodynamics and Clinical Effects

Detailed information regarding the HOPE trial is presented in the *Pharmacodynamics and Clinical Effects* subsection of Altace labeling. King requests that FDA confirm that it will "continue to approve ramipril products for the treatment of hypertension only with complete and accurate label information regarding the outcomes associated with treating hypertensive and non-hypertensive patients as described in the label information obtained from the HOPE trial" (Petition at 1 to 2).

As discussed in section II.A of this response, given that the effect of ramipril on the composite outcome of myocardial infarction, stroke, or death from cardiovascular causes did not materially differ among patients with and without a history of hypertension treated with ramipril, it is difficult to assert that the HOPE trial provides cardiovascular outcomes data specific to the hypertension indication. Accordingly, the HOPE information presented in the *Pharmacodynamics and Clinical Effects* subsection of Altace labeling can be omitted from the labeling of a generic ramipril product that seeks approval for the treatment of hypertension without rendering that product less safe or effective for the treatment of hypertension.

3. Dosage and Administration

Information in the DOSAGE AND ADMINISTRATION section of Altace labeling for the HOPE indication is not necessary for the safe and effective use of ramipril products for the treatment of hypertension. The dosing instructions for treatment of hypertension describe a recommended initial dose and state that "[d]osage should be adjusted according to the blood pressure response." The labeling further states that the "usual maintenance dosage range is 2.5

[22] See HOPE Study article at Table 1.

to 20 mg per day administered as a single dose or in two equally divided doses." The dosing regimen described for the HOPE indication reflects the specific dosing algorithm used in the HOPE trial rather than dosing adjustment based on blood pressure response. The dosing instructions for the HOPE indication state: "ALTACE should be given at an initial dose of 2.5 mg, once a day for 1 week, 5 mg, once a day for the next 3 weeks, and then increased as tolerated, to a maintenance dose of 10 mg, once a day. If the patient is hypertensive or recently post myocardial infarction, it can also be given as a divided dose." Although instructions are provided for administering ramipril as a divided dose in hypertensive patients for the HOPE indication, omission of the HOPE dosing information would not make ramipril products less safe or effective for the treatment of hypertension (the dosage information for the hypertension indication also describes administration of ramipril as a divided dose).

4. Adverse Reactions

Finally, we address the safety data from the HOPE trial included in the ADVERSE REACTIONS section of Altace product labeling. The adverse events described are cough, hypotension or dizziness, and angioedema. All of these adverse events are adequately described in other sections of Altace product labeling, and the incidence of cough and angioedema reported in the HOPE trial was similar to that described in other ramipril clinical trials. Thus, omitting the safety information from the HOPE trial described in the ADVERSE REACTIONS section of Altace product labeling would not be expected to have an impact on the safe use of ramipril for the treatment of hypertension.

C. Omission of the HOPE Indication From Labeling of a Generic Ramipril Product Seeking Approval for the Treatment of Hypertension Is Not Inconsistent with the Approach Described in the Draft Hypertension Guidance

In March 2008, FDA issued a draft guidance for industry on *Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims* (Draft Hypertension Guidance). The Draft Hypertension Guidance, distributed for comment purposes, reflects discussion at the June 15, 2005, and April 26, 2006, meetings of FDA's Cardiovascular and Renal Drugs Advisory Committee regarding the development of class labeling for antihypertensive drug products to describe "clinical benefits related to cardiovascular outcome expected from lowering blood pressure" (Draft Hypertension Guidance at 2). The Draft Hypertension Guidance proposes standard language to be substituted for the hypertension indication and a standard approach to describing cardiovascular outcome data from studies "demonstrating reductions in cardiovascular risk in patients with hypertension" (p. 5). Additional drug-specific or class-specific labeling to refer to specific studies supporting effects on cardiovascular events would be permitted when clearly supported by clinical data, but the proposed standard language is intended for all antihypertensive drugs, whether or not they have specific controlled trial data. Through the development of standardized labeling as proposed in the draft guidance, FDA seeks to encourage the appropriate use of antihypertensive drugs "by making the connection between

lower blood pressure and improved cardiovascular outcomes more explicit in labeling" (p. 1).[23] Again, this is a general conclusion applicable to all antihypertensive drugs.

You suggest that the HOPE trial "provides the type of outcomes information contemplated by the guidance" (Petition at 9). In support of this assertion, you note that ramipril is one of the drug products within the class of ACE inhibitors for which the guidance indicates that there is "specific outcome data in either placebo-controlled or active-controlled [trials] as either primary or secondary treatment" (see Draft Hypertension Guidance at 6, Table 1).

We note that the Draft Hypertension Guidance does not specify which trials contributed the specific outcome data for particular drug products listed in bold typeface in Table 1. Although at one time the HOPE study was believed to be pertinent, the HOPE study was not intended to be a study of blood pressure reduction. Accordingly, whether the HOPE trial provides the "specific outcome data" described by the Draft Hypertension Guidance is questionable. As discussed in section II.A of this response, the use of ramipril in the HOPE trial was not necessarily to control blood pressure and differs in this respect from the cardiovascular outcomes trials described in the Draft Hypertension Guidance. Further, the effect of ramipril on cardiovascular outcomes in the HOPE trial was not attributed primarily to a reduction in blood pressure — the focus of the Draft Hypertension Guidance.

More critical is the fact that the premise of the Draft Hypertension Guidance is not drug or drug-class specific, but rather represents a conclusion about the benefit of lowering blood pressure with any drug. Indeed, the emphasis of the guidance is the "consistently favorable effects" on cardiovascular outcomes across many antihypertensive drug classes attributable to a reduction in blood pressure (p. 3). The availability of any particular product-specific data is of interest, but drug-specific cardiovascular outcomes data are not necessary to support safe and effective introduction of the class labeling described in the guidance. The absence of such outcome-specific data from ramipril product labeling would not render a generic ramipril product less safe or less effective than Altace for the treatment of hypertension. Indeed, current Altace labeling does not reference the HOPE trial as part of its hypertension claim.

You further assert that "the addition of the HOPE label information served to further inform the treatment of hypertension by adding outcomes, and thus *increase* the safe and effective treatment of hypertension as contemplated by FDA and the advisory committees described above..." (Petition at 10) (emphasis in original). However, as noted, the information regarding the HOPE trial in Altace labeling is not directed to treatment of hypertension or clinical benefits related to cardiovascular outcome expected from lowering blood pressure.

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[23] We note that FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.

III. CONCLUSION

We have concluded that exclusion of information in Altace product labeling related to the HOPE indication does not render a generic ramipril drug product less safe or effective for the remaining conditions of use. Accordingly, we deny your request that FDA disallow subsequent ANDA and 505(b)(2) applicants from submitting a statement pursuant to section 505(j)(2)(A)(viii) or 505(b)(2)(B) of the Act with respect to the '469 patent.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research